The addition of VI (L-522132-0-0) to the vagus nerve had no effect on the action potential. Similarly VIII (L-591515-0-4) had an insignificant effect. The addition of VII (L-584424-0-1) produced a slight decrease in the amplitude of the action potential.

Although limited in scope, these experiments suggest that both the pyridine and pyrimidine ring of pyrithiamine are required for its effect on the action potential of the non-myelinated nerve fibers of the rabbit vagus nerve. The greater sensitivity of the nerve to IV compared to II (pyrithiamine) may be a reflection of ease of transport since this agent with an ethyl group on the 1 position of the pyrimidine ring would be more lipid soluble than pyrithiamine with a methyl group on this position.

The high correlation between the effect of these analogs of thiamine on the electrical activity of the nerve fibers and their effectiveness in producing polyneuritis in animals[6] suggests that a further investigation with this in vitro system may be useful in elucidating the etiology of the neuropathy that is associated with a thiamine deficiency state.

Zusammenfassung. Der Einfluss einer Anzahl Thiaminanaloga auf die elektrische Aktivität des Vagus wurde untersucht. Das Äthylanalogon des Pyrithiamins hatte mindestens die zehnfache Wirkung des Pyrithiamins auf die Erhöhung der Amplitude des Aktionspotentials. Die Resultate stimmen gut überein mit der Fähigkeit dieser Antimetabolite, in vivo Polyneuritis hervorzurufen.

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Potentiation of the Cerebral Vascular Action of Bradykinin by the 'Bradykinin Potentiating Factor' (BPF) in the Dog

The vasodilating effect of bradykinin upon the cerebral vessels has already been described[1–3]. It has also been indicated that bradykinin may play a role in the physiopathological control of the cerebral circulation[1,2]. On the other hand, the 'bradykinin potentiating factor' (BPF), a purified extract from the venom of *B. jararaca*, has been shown to act in vitro as well as in vivo[4].

Eight dogs, weighing 18 to 22 kg, were employed in the experiments. The animals were anaesthetized with morphine (2 mg/kg, s.c.) and chloralose (90 mg/kg, i.v.) and the intra-cranial pressure recorded by means of a catheter introduced in a cephalad direction through the external jugular vein[5]. The tracings of the intra-cranial blood pressure together with the femoral arterial blood pressure and the respiration were simultaneously recorded in a Grass, 6-channel Polygraph. Synthetic bradykinin (BRS 640 Sandoz), kallidin (KL 695 Sandoz), eledoisin (ELD 950 Sandoz) and histamine were administered through a small catheter, placed into the lingual artery and directed towards the carotid artery. Drugs were diluted in saline and 0.2 ml of this solution followed by 0.2 ml saline were injected each time. The same route was used for the administration of BPF (10 mg in 0.3 ml of saline). Though by slow injection no effects could be observed, when the factor was injected quickly, a moderate fall in arterial blood pressure together with mild acceleration in respiratory movements and increase of 3 to 5 cm H_2O in the intracranial venous pressure occurred. Consequently, in all experiments presented in continuation, the factor was injected slowly, in about 30 sec (0.3 ml).

The intra-carotideal injection of bradykinin in doses varying from 0.01 to 0.1 μg, according to the sensitivity of the preparation, produced a clear-cut rise in the intracranial blood pressure, ranging from about 1 to 6 cm H_2O, without any change in the systemic blood pressure and respiration (Figure 1). Similar effects were obtained with the other three agonists, kallidin being in all cases more potent than bradykinin, and histamine being always less effective than either agent; eledoisin was more potent in some experiments and less in others (Table). Neat dose-

Effect of BPF upon the cerebral vascular action of bradykinin, kallidin, eledoisin, and histamine

Experiment number		Increase in intra-cranial venous pressure (cm H_2O)[a]		Potentiation ratio			
		before	after	BK	KL	ELD	H
I	Bradykinin (0.01 μg)	1.25	7.20	5.7	–	–	–
	Histamine (0.4 μg)	5.30	3.12	–	–	–	0.6
II	Bradykinin (0.01 μg)	1.25	2.50	2.0	–	–	–
	Histamine (0.03 μg)	1.25	1.88	–	–	–	1.5
III	Bradykinin (0.1 μg)	5.95	9.68	1.6	–	–	–
	Histamine (1 μg)	5.30	5.30	–	–	–	1.0
IV	Bradykinin (0.02 μg)	5.30	14.20	2.7	–	–	–
	Eledoisin (0.04 μg)	4.68	10.30	–	–	2.2	–
	Kallidin (0.02 μg)	8.10	14.28	–	1.8	–	–
V	Bradykinin (0.01 μg)	5.61	18.80	3.3	–	–	–
	Eledoisin (0.05 μg)	5.30	3.75	–	–	0.7	–
VI	Bradykinin (0.1 μg)	4.68	9.05	1.9	–	–	–
	Eledoisin (0.1 μg)	7.20	8.41	–	–	1.2	–
	Kallidin (0.1 μg)	12.45	10.30	–	0.8	–	–
VII	Eledoisin (0.1 μg)	12.20	9.69	–	–	0.8	–
	Kallidin (0.005 μg)	5.61	9.35	–	1.7	–	–
VIII	Eledoisin (0.2 μg)	7.80	6.75	–	–	0.9	–
	Kallidin (0.005 μg)	3.12	12.45	–	4.0	–	–
Mean potentiation ratio				2.9	2.1	1.2	1.0

[a] The values presented refer to the increase in intra-cranial venous pressure due to the drugs injected, respectively, during the 10 min time interval preceding (before) and the 10–20 min interval following (after) the intra-carotideal administration of BPF (10 mg).

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effect relationships were observed (Figure 2). In two experiments, where bradykinin and histamine were also injected intravenously, larger doses of about 0.5 to 3.0 μg/kg of bradykinin were necessary to induce comparable effects upon the intra-cranial vessels, histamine being roughly equipotent with bradykinin. In these cases, however, a fall in systemic blood pressure and stimulation of respiratory movements were also observed, in agreement with CARPI and CORRADO[2].

The effects of bradykinin were clearly enhanced in all experiments by the intra-carotideal administration of BPF; kallidin was also potentiated by BPF in three out of four experiments. The potentiation ratio of bradykinin ranged from 1.6 to 5.7 and for kallidin from 0.8 to 4.0. The actions of eledoisin and histamine were practically unaffected (Table).

As indicated above, the potency ratio between bradykinin and histamine was nearly 1 when the drugs were administered intravenously; this ratio was shifted to 10, in favour of bradykinin, when the intra-carotideal route was employed.

This difference may be due to the fact that bradykinin is much more rapidly destroyed by plasma than histamine[6]. The potentiating effect of BPF may be similarly explained by the inhibitory action of the factor upon the kinin inactivating enzymes in the plasma[7]. The simultaneous use of the intra-carotideal route plus the potentiation by BPF, mimicks the local liberation of endogenous peptides, as it probably occurs in physiopathological conditions[8,9].

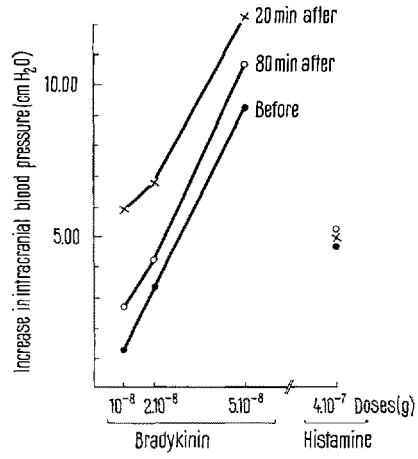

Fig. 2. Graphical representation of one experiment performed on a dog, 18 kg, anaesthetized with morphine (2 mg/kg, s.c.) and chloralose (90 mg/kg, i.v.). Three increasing doses of bradykinin (0.01, 0.02 and 0.05 μg) were injected in three successive series, as follows: before (•); 20 min (x) and 80 min (o) after the administration of BPF (10 mg). Note the linear dose-effect relationship before the injection of BPF and the clear cut potentiation of the action of bradykinin injected 20 min after the factor – the potentiation is greater with smaller doses of the polypeptide. After 80 min the potentiating effect is still present. The effects of three control injections of histamine (0.4 μg) are also represented in the Figure; it can be seen that the sensitivity of the preparation remained unchanged during the experiment. Drugs were diluted in saline and injected via the intra-carotid route.

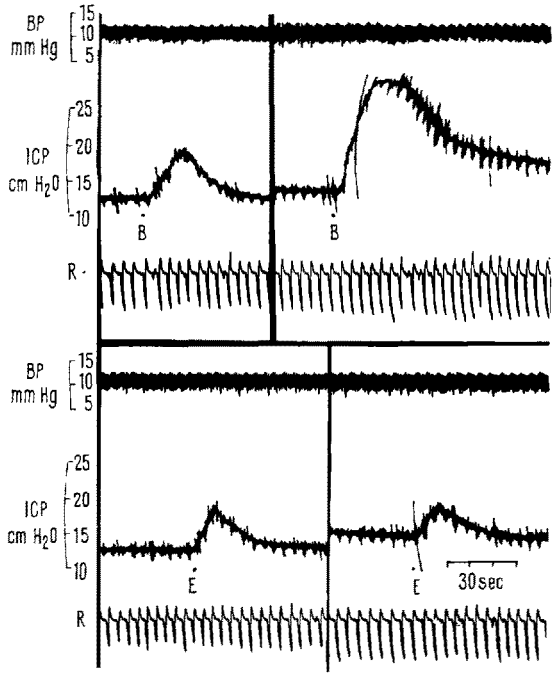

Fig. 1. Effect of 'bradykinin potentiating factor', BPF, upon the vasodilating action of bradykinin (upper panels) and eledoisin (lower panels) on the cerebral circulation. Dog, 20 kg, anaesthetized with morphine (2 mg/kg, s.c.) plus chloralose (90 mg/kg, i.v.). Left panels: increase in the intra-cranial venous pressure produced by 0.01 μg of bradykinin (B) and 0.05 μg of eledoisin (E), injected into the carotid artery. Right panels: as above, following an intra-carotideal injection of 10 mg of BPF. ICP: intra-cranial venous pressure, measured in the external jugular vein. BP: arterial blood pressure in the left femoral artery. R: respiration. Drugs were diluted in saline.

Zusammenfassung. Die gefässerweiternde Wirkung von Bradykinin und Kallidin auf den cerebralen Kreislauf wurde durch den «BPF»-Faktor aus Schlangengift erheblich potenziert, während sie bei Eledoisin und Histamin nur wenig verändert wurde.

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